(22) Septic shock

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AFELIMOMAB

JL VINCENT MD, PhD, Department of Intensive Care, Erasme Hospital, Free University of Brussels, Belgium

SUMMARY Tumour necrosis factor-α (TNF-α) is well established as a key mediator in the inflammatory response seen in various disease processes including sepsis. TNF-α is involved in virtually all features of septic shock and multiple organ failure. Anti-TNF-α strategies are thus appealing and have been effective at reducing inflammation and morbidity in certain conditions including rheumatoid arthritis and Crohn's disease. Afelimomab is the F(ab')$_2$ fragment of a murine anti-TNF-α antibody, and has been evaluated in clinical trials in septic patients. The results suggest that the drug is well tolerated, and may be of benefit in certain groups of patients with sepsis. A large, randomised, clinical trial of afelimomab in patients with severe sepsis has recently been completed and the results are eagerly awaited. More work is necessary to identify a means of selecting which patients are most likely to benefit from this type of therapy in sepsis. (*Int J Clin Pract* 2000; **54(3)**: 190-193)

Afelimomab is one of a range of drugs developed to act against the cytokine, tumour necrosis factor-α (TNF-α). TNF-α is a key mediator in the pathogenesis of local and systemic inflammatory responses in disease processes as apparently divergent as sepsis,[1] rheumatoid arthritis,[2] inflammatory bowel disease,[3] and multiple sclerosis.[4] Strategies directed against TNF-α have thus been developed for use in these conditions. In this review we will discuss the role of TNF-α in inflammation, particularly concentrating on its actions in sepsis. We will then discuss the various strategies by which its activity can be blocked, before focusing on the clinical sepsis trials involving afelimomab, a monoclonal anti-TNF-α antibody.

TUMOUR NECROSIS FACTOR

TNF-α (formerly also called cachectin) is one member of a family of cytokines that also includes TNF-β (lymphotoxin-α), Fas ligand, TNF-related apoptosis-inducing ligand (TRAIL), nerve growth factor, and CD40 ligand.[5] The TNF family is primarily involved in the regulation of cell proliferation and apoptosis, but TNF-α has additional pro-inflammatory properties, recruiting and activating neutrophils, macrophages and lymphocytes and stimulating the release of a host of other pro-inflammatory cytokines and acute phase proteins.

TNF-α is expressed as a 26 kDa polypeptide protein which is cleaved into its soluble 17 kDa form by a specific matrix metalloproteinase, TNF-α converting enzyme. TNF-α binds to two distinct TNF receptors, which trigger different cellular events. Both receptors are present on many cells, but one is usually dominant. The precise roles of the two receptors are far from clear.[5] TNFR1 (p55) is believed to be primarily responsible for TNF-α's pro-inflammatory properties, while TNFR2 (p75), although having little inflammatory properties of its own, may act to potentiate TNFR1 activity. The synthesis of TNF-α is tightly controlled at various levels including gene transcription and translation.[6] In addition, by stimulating the shedding of TNF receptors,[7] and the production of various anti-inflammatory compounds which inhibit TNF-α production,[8] TNF-α effectively down-regulates its own activity.

TNF-α is an essential mediator in the host defence against infection and acute inflammation,[9-11] but when there is excessive systemic release, as in septic shock, TNF-α becomes foe rather than friend. Evidence for a key role of TNF-α in septic shock is provided in three ways (Table 1). First, high serum levels of TNF-α have been reported in patients with sepsis,[12-15] and raised levels have been correlated with outcome,[16-19] although the presence of persistently raised levels is more likely to be associated with increased mortality than any one single raised level.[15] Systemic release of TNF-α occurs soon after the injection of endotoxin into healthy volunteers,[20] with TNF-α detectable in the blood about 1 hour after endotoxin infusion, reaching peak levels at 1.5 to 2 hours, and falling to baseline by 3 hours. However, not all studies have reported raised serum levels of TNF-α in patients with sepsis,[21,22] and this finding may represent association rather than causation. Second, injection of TNF-α into animals reproduces many of the haemodynamic effects seen in endotoxic or septic animals.[23-25] Similarly, injection of TNF-α in healthy volunteers[26-30] and in cancer patients[31-33] induces the fever, hypotension, metabolic response, coagulation activation, and release of other cytokines, seen in patients with sepsis. Third, attempts to block TNF-α activity have been associated with improved survival in animal models of septic shock,[34,35] although were less effective in peritonitis.[10] Anti-TNF-α strategies have also been shown to be effective at suppressing the Jarisch-Herxheimer reaction that occurs in patients with louse-borne relapsing fever after antibiotic administration.[36]

ANTI-TNF STRATEGIES

Strategies aimed at blocking the activity of TNF-α have primarily focused on direct inhibition of free TNF-α with anti-TNF-α antibodies or on the administration of soluble TNF receptors to mop up circulating TNF-α.

ADDRESS CORRESPONDENCE TO: Professor JL Vincent, Erasme University Hospital, Route de Lennik 808, 1070 BRUSSELS, Belgium

Table 1: Factors supporting a key role for TNF-α in sepsis

- TNF-α levels are frequently raised in sepsis and septic shock, and high levels have been correlated with high mortality
- Administration of TNF-α to human volunteers reproduces many of the clinical signs of sepsis
- Anti-TNF-α antibodies are protective in animal models of sepsis

Anti-TNF-α antibodies

Anti-TNF-α antibodies have been shown to reduce mortality and morbidity in various animal models of acute and severe sepsis.[34,35,37] Anti-TNF-α antibodies have also had beneficial effects in animal models of other inflammatory conditions including acute pancreatitis,[38] rheumatoid arthritis,[39] and Crohn's disease.[40]

Various anti-TNF-α antibodies have been tested clinically in patients with severe sepsis. The first of these, CB0006 a murine monoclonal antibody, was well tolerated,[41] had beneficial effects on ventricular function,[42] and a phase II trial suggested an improved survival in patients with the highest TNF-α levels.[43] Another murine antibody (Bay x1351) was studied in three large multicentre, randomised, clinical trials. The first of these (NORASEPT I) showed a reduction in 3-day mortality,[44] and the second (INTERSEPT) showed a trend to reduced 28-day mortality in patients with septic shock.[45] However, the third study (NORASEPT II) could not demonstrate any beneficial effects of the anti-TNF-α treatment on survival or resolution of organ failure.[46]

Afelimomab

Afelimomab (MAK 1 95F, Knoll, Ludwigshafen) is the $F(ab')_2$ fragment of a murine immunoglobulin monoclonal antibody directed against human TNF-α. It is highly species specific, neutralising human and chimpanzee TNF-α both in vivo and in vitro.[47,48] Pharmacokinetically, afelimomab follows a two-compartment model with a first serum half-life of about 3 hours and a second half-life of about 30 hours for a dose of 1 mg/kg.[48] For the same dose, the volume of distribution was estimated at about 70 ml/kg and the clearance at about 10 ml/h/kg.[48] As a fragment rather than the complete antibody, afelimomab may have reduced immunogenicity.[49] Indeed, in clinical trials in sepsis patients human antimurine antibodies occurred in 40% of patients treated with afelimomab,[49] compared with 98% of patients treated with the complete antibody CB0006. Adverse events reported with the use of complete anti-TNF-α antibodies have been related to the development of human antimurine or anti-chimeric antibodies, and have included hypersensitivity reactions and rare cases of drug-induced lupus.[50] There have been no reports in the literature of similar adverse events with afelimomab. In addition, as a fragment, the tissue penetration of afelimomab may be greater than with complete antibodies.[49] As TNF-α production is greatest at the site of inflammation,[51,52] this feature may be important in enhancing efficacy.

Afelimomab has now been tested clinically in more than 3000 patients with severe sepsis and septic shock (Table 2). In a phase I clinical trial, afelimomab was well tolerated and caused a sustained rise in blood pressure.[48] In a phase II, randomised, open-label study in Europe, involving 122 patients with severe sepsis, afelimomab was again well-tolerated, and retrospective stratification by IL-6 levels suggested a beneficial dose-dependent effect of afelimomab on mortality in patients with IL-6 levels >1000 pg/ml.[49] In this subgroup of patients, day 14 mortality was reduced from 80% in the placebo group to 35% in patients treated with the highest dose (1 mg/kg) of afelimomab. IL-6 has been suggested as a potential marker of the severity of sepsis.[14,53] Based on the results from the phase II study,[49] a phase III study, RAMSES (Randomised placebo-controlled trial of the Anti-TNF antibody fragment MAK 1 95F in hyperinflammatory response in SEvere Sepsis), was designed, whereby patients were stratified on the basis of

Table 2: Clinical trials in sepsis patients using afelimomab

Reference	Study design	Patients included	No of patients	Summary of results
Boekstegers *et al.*[48]	Phase I	Severe sepsis	20	Well-tolerated. Increased blood pressure, and reduced requirement for catecholamines.
Reinhart *et al.*[49]	Phase II	Severe sepsis or septic shock	122	Well tolerated. Retrospective analysis suggested a dose dependent reduction in mortality with afelimomab when IL-6 levels >1000 pg/ml.
Reinhart *et al.*[54]	Phase III	Severe sepsis. Stratified for randomisation or not on basis of IL-6 levels.	944	Trend towards reduced mortality, earlier resolution of organ failure and reduction of IL-6 levels.
MONARCS	Phase III	Severe sepsis.	>2000	Results awaited

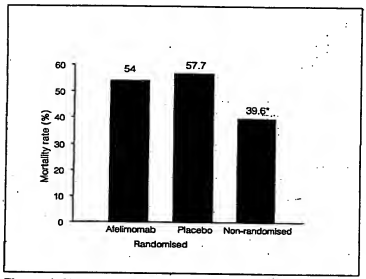

Figure 1. Mortality rates in RAMSES study showing increased mortality in patients with high IL-6 levels and trend to reduced mortality in patients treated with afelimomab. *P<0.001 non-randomised versus randomised patients

their IL-6 levels, using a rapid bedside test to identify patients with an IL-6 level >1000 pg/ml. In this study,[34] conducted in 10 European countries and Israel, patients with a positive IL-6 test were randomised to receive either afelimomab (1 mg/kg) or placebo. Patients with a negative IL-6 test were not randomised but were followed for survival for 28 days. The trial was discontinued after an interim analysis suggested that the planned sample size would be too small to show any statistically significant difference in mortality. Patients with a positive IL-6 test had a significantly higher mortality rate than those in the IL-6 negative group, supporting the use of this cytokine as a marker of sepsis severity (Figure 1). An epidemiological study (SELECT) is currently underway in Europe and the USA to confirm the potential role of IL-6 as a sepsis marker.

A second phase III study (MONARCS) using afelimomab has recently been completed in the USA and Canada). In this study, unlike RAMSES, although the IL-6 test was performed on all included patients, all patients were randomised to treatment or placebo regardless of the IL-6 test result. This study enrolled more than 2000 patients, and the results are awaited eagerly.

TNF receptors

An alternative approach to TNF-α inhibition is to administer TNF receptors. A clinical study with TNFR2, involving 141 patients with septic shock, was associated with an increased mortality in patients treated with the highest dose.[35] Although interpretation of these results is difficult given the small number of patients, further development of this molecule for use in sepsis is definitely compromised. A randomised, placebo-controlled trial of TNFR1 in the USA and Europe, which included 498 patients, gave more promising results with a trend towards reduced mortality in patients with severe sepsis treated with the highest dose (0.083 mg/kg) of TNFR1.[36] However, a large phase III trial could not demonstrate any significant improvement in outcome (unpublished data).

CONCLUSION

Although major advances have been made in our understanding of the inflammatory response to sepsis and the complex pathways involved, there is still much that remains unclear. TNF-α is a key mediator of inflammation, and anti-TNF-α antibody therapies have been effective in reducing inflammation and morbidity in clinical trials in various, well-defined inflammatory conditions including rheumatoid arthritis[37] and Crohn's disease.[38] However, in sepsis, the findings have not been so convincing. There are many reasons for this, including the heterogeneous nature of the intensive care population in whom these studies are conducted, difficulties in definition of sepsis, and the complexities of the sepsis response making it unlikely that any one treatment will help all patients at all times.[39] In addition, TNF-α is an essential part of the host response and the use of anti-TNF-α strategies in the wrong patient or at the wrong time may do more harm than good. Further work is necessary to identify markers that can assist in characterising patients for trial inclusion; IL-6 may be one such marker. Anti-TNF-α strategies, such as afelimomab, may yet prove valuable in the treatment of carefully selected patients with severe sepsis; the challenge is to direct these agents at those patients most likely to benefit from them.

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